Analysis of a Large-Scale Screening of Mitochondrial DNA m.1555A>G Mutation in 2417 Deaf–Mute Students in Northwest of China

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The ancient Silk Road (also called “Northwest Silk Road”) in Northwest China, starting from Xian, passes through Gansu, Xinjiang, Central Asia, West Asia, and the land passage connecting the Mediterranean countries. The aim of the present study was to determine the frequency of mitochondrial DNA 12SrRNA m.1555A>G mutation in a total of 2417 cases of nonsyndromic deaf–mute patients representative of the general population of Shaanxi, Gansu, Qinghai, Ningxia, and Xinjiang along the Silk Road. Enzyme digestion and direct sequencing were applied to identify sequence variations. The carrier frequency of mitochondrial DNA 12SrRNA m.1555A>G mutation was estimated to be 5.21% (126/2417) in the studied population. In detail, the carrier frequency of Uighur and Hui was 1.62% (3/185) and 3.29% (10/304), respectively, compared with 6.09% (113/1856) that of Han. There was a statistically significant difference between Uighur and Han (chi-square test, \( \chi^2 = 6.437, p = 0.011 < 0.05 \)), whereas no significant difference in m.1555A>G mutation spectrum or prevalence of mitochondrial DNA 12SrRNA was found between Uighur and Hui or Hui and Han. In the 126 m.1555A>G mutation carriers, 52 cases were found to have a clear history of using aminoglycoside antibiotics. Results suggested that the application of aminoglycoside antibiotics in this region is an important reason for higher incidence of m.1555A>G mutation in the deaf–mute population.

Introduction

Severe or profound deafness occurs in ~1 per 650 newborns (Mehl and Thomson, 2002); 61%–66% of the children are affected by the age of 4 because of genetic factors (Fortnum et al., 2001; Kennedy and McCann, 2004; Nance et al., 2006). The mitochondrial DNA 12S rRNA m.1555A>G mutation associated with aminoglycoside antibiotic-induced deafness attracts significant attention (Prezant et al., 1993; Fischel-Ghodsian et al., 1995; Usami et al., 1997; Malik et al., 2003; Kupka et al., 2004; Wu et al., 2007; Guo et al., 2008). The m.1555A>G mutation is located in a highly conserved region of the 12S rRNA that is an essential part of the decoding site of the ribosomal subunit. The nucleotide at position 1555 in the human 12S rRNA in wild-type cells is A, which, when mutated to a G, pairs with the C at position 1494. This transition makes the secondary structure of the RNA resemble more closely the corresponding region of bacterial 16S rRNA. This new G-C pair in 12S rRNA is also expected to create a binding site for aminoglycosides, which facilitates interaction with these drugs (Guan, 2004). And finally, the proteins synthesized in the mitochondrion, which are essential for cell respiration, decreases. In the United States, 10% of the patients with aminoglycoside antibiotic-induced deafness carried the mitochondrial DNA 12SrRNA m.1555A>G mutation (Price, 1986), whereas in Spain, 27% of familial nonsyndrome deafness cases was related to the m.1555A>G mutation and these patients suffered progressive hearing loss with age without application of aminoglycoside antibiotics (Estivill et al., 1998). A number of racial populations over the world have been screened for the locus mtDNA m.1555A>G, again indicating markedly different mutation rates among different geographic or racial origins. In Caucasians living in Europe or America, the m.1555A>G mutation rates of sporadic patients are 0.6%–2.4% (Li et al., 2004; Berrettini et al., 2008; Konings et al., 2008; Rydzanicz et al., 2009); in Mongoloids living in East and Southeast Asia, a rate of 1.6%–8.56% was observed (Pandya et al., 1999; Oshima et al., 2001; Li et al., 2004; Guo et al.,...
varieties of aminoglycoside antibiotics can lead to about 22% of deaf patients in only a district of Shanghai, of which 28% patients have other family members who suffer deafness at the same time (Hu et al., 1991). The economic and health situations of the cities in Northwest China are poor compared with Shanghai and other developed cities, and the use of aminoglycoside antibiotics more widely spread in the absence of adequate monitoring. So, the authors believed that the widespread use of aminoglycoside antibiotics in this district is another cause of the high m.1555A>G mutation frequency. In 441 binaural hearing screening-passed subjects recruited in this study, only one carrier was detected, with a frequency of 0.23%. We suggest that if the babies at birth are subjected to m.1555A>G mutation screening, to avoid the use of aminoglycosides drugs, positive subjects may not become patients, as well as the incidence of deafness will decline (Wang et al., 2007).

However, it is interesting to note that the m.1555A>G mutation frequency of Uighur is 1.62% (3/185), which is considerably lower than that of Hui or Han in this population. Xinjiang is located in the eastern part of Central Asia and Central Asia, western China, and acts as an important section of the ancient “Silk Road” and the corridor of the East–West race in Eurasia. In history, Xinjiang experienced a complex cultural formation and migration of many races. Molecular geneticists have proposed a theory of human genetic mixing origins in this area so that it has played a pivotal role in the history of humankind, having witnessed numerous waves of migration of different peoples at different times. Mitochondrial haplotypes in modern Uighur have been reported as follows: 34% containing haplotypes commonly found in west Eurasian, and 55% containing haplotypes commonly found in east Eurasia (Lalueza-Fox et al., 2004; Quintana-Murci et al., 2004). Thus, ethnic factors may be the main reason for causing the mutations in the Xinjiang Uighur patients to be of lower incidence than in other nations.

In conclusion, mitochondrial DNA m.1555A>G is the hotspot mutation of deaf population in Northwest China. Active genetic counseling and intervention and avoiding usage of aminoglycoside antibiotics in patients and their maternal family members can effectively prevent the occurrence of deafness.

Acknowledgments

This work was supported by grants from the National High-Tech R&D Program of China (No. 2006AA02Z181), the National Natural Science Foundation of China (Key Program, No. 30830104; General Program No. 30672310, 30771857, and 30771203), the National Program on Key Basic Research Project of China (No. 2007CB507400), Beijing Municipal Natural Science Foundation (Major Program, No. 7070002), the National Science and Technology Pillar Development Program in the Eleventh Five-year Plan Period (No. 2006BAI02B06 and 2007BAI18B12), the Natural Science Foundation of Gansu Province (No. 096RJZA074), as well as Gansu Technology Research and Development Major Project (No. 0805TCYA004).

Disclosure Statement

The authors declare that they have no competing interests.

References


